

**FRAILITY IN CARDIOVASCULAR PATIENTS: AN EMERGING RISK FACTOR WITH CLINICAL SIGNIFICANCE**

**D. Gospodinov<sup>1</sup>, L. Hadzhilieva<sup>1</sup>, N. Gerasimov<sup>2</sup>**

<sup>1</sup> Faculty of Medicine, Trakia University – Stara Zagora, Bulgaria

<sup>2</sup> Medical College, Trakia University – Stara Zagora, Bulgaria

**Abstract**

Frailty has emerged as a clinically relevant syndrome in cardiovascular medicine, characterized by reduced physiological reserve and increased vulnerability to stressors. It is increasingly recognized as an independent predictor of adverse outcomes in patients with cardiovascular disease, including heart failure, coronary artery disease, and valvular heart disease.

This narrative review examines the pathophysiology, clinical implications, and prognostic value of frailty in cardiology. Special attention is given to its role in risk stratification, therapeutic decision-making, and outcomes following interventional procedures. Frailty is associated with increased mortality, higher rates of hospitalization, reduced tolerance to guideline-directed therapy, and poorer procedural outcomes. Despite its clinical importance, it remains underassessed in routine practice.

The integration of frailty assessment into cardiovascular care may improve individualized treatment strategies and clinical outcomes.

**Keywords:** *frailty, cardiovascular disease, heart failure, elderly patients, risk stratification, sarcopenia*

**CORRESPONDENCE**

Nikolay Gerasimov

e-mail: nikolay.gerasimov@trakia-uni.bg

**METHODS**

**Aim**

The aim of this narrative review is to evaluate frailty as an independent risk factor in cardiovascular patients and to assess its impact on clinical outcomes and therapeutic strategies.

**Design**

Narrative literature review focused on clinically relevant evidence.

**Data sources and search strategy**

Literature search was conducted in: PubMed/MEDLINE; Scopus; Web of Science.

**Timeframe:** 2015–2025

**Search terms:**

“frailty”, “cardiovascular disease”, “heart failure”, “elderly”, “sarcopenia”, “TAVI”, “outcomes”, “mortality”

**Inclusion criteria:**

- randomized clinical trials;
- meta-analyses;
- observational cohort studies;
- guideline and consensus documents.

**Exclusion criteria:**

- case reports;
- studies without clinical endpoints;
- non-English publications.

**Scope of the review**

Identified: around 160 publications

Included: 20 key sources

### 1. Introduction

Frailty is increasingly recognized as a major determinant of outcomes in cardiovascular disease. It reflects a state of reduced physiological reserve and impaired ability to respond to stressors such as acute illness, hospitalization, or invasive procedures [1]. In cardiology, frailty is particularly relevant due to the aging population and the high prevalence of multimorbidity. A substantial proportion of patients with heart failure, coronary artery disease, and valvular heart disease meet criteria for frailty, especially in advanced age groups [2]. Unlike chronological age, frailty provides a more accurate estimate of biological vulnerability. Patients with similar diagnoses and comparable clinical parameters may have significantly different outcomes depending on their frailty status. This has led to the recognition of frailty as an independent predictor of mortality, hospitalization, and functional decline [1].

Frailty also influences therapeutic decision-making. Frail patients are less likely to tolerate guideline-directed medical therapy and more prone to adverse effects. In addition, outcomes following interventional procedures such as transcatheter aortic valve implantation are strongly affected by frailty status [3].

Despite its clinical importance, frailty remains underrecognized and inconsistently assessed in routine practice. Standard cardiovascular risk models do not fully account for its impact, which may lead to underestimation of risk in vulnerable patients. The purpose of this review is to examine the mechanisms, clinical implications, and prognostic value of frailty in cardiovascular patients and to explore its role in modern cardiology.

### 2. Definition and Phenotypes of Frailty

Frailty is defined as a clinical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors, resulting in a higher risk of adverse outcomes. It reflects cumulative decline across multiple organ systems rather than impairment of a single pathway [4].

Two main conceptual models of frailty are used in clinical practice: the phenotype model and the deficit accumulation model. The phenotype model, described by Fried et al., defines frailty based on five clinical criteria: unintentional weight loss, muscle weakness, exhaustion, slow gait speed, and low physical activity. Patients meeting three or more criteria are classified as frail, while those with one or two are considered pre-frail [4]. This model is simple, clinically intuitive, and widely used in research and practice.

The deficit accumulation model, developed by Rockwood and colleagues, conceptualizes frailty as the result of accumulated health deficits. These include comorbidities, symptoms, functional impairments, and cognitive decline. The frailty index is calculated as the proportion of deficits present out of a predefined list, providing a continuous measure of vulnerability rather than a categorical classification [5]. These two models capture different aspects of frailty. The phenotype approach focuses on physical performance and functional decline, while the deficit model reflects overall health status and complexity. In cardiovascular patients, both models have been shown to predict adverse outcomes, although the choice of assessment tool often depends on clinical context. In addition to these models, several practical tools have been developed for routine use. The Clinical Frailty Scale (CFS) is a simple bedside tool that categorizes patients based on functional status and dependence. It is widely used in cardiology due to its ease of application and strong prognostic value [6]. Sarcopenia is a central component of frailty and refers to the loss of skeletal muscle mass and strength. It contributes directly to reduced physical performance and is strongly associated with worse outcomes in cardiovascular disease. Although not synonymous with frailty, it represents a key biological substrate of the syndrome. Importantly, frailty is a dynamic condition. Patients may transition between states of robustness, pre-frailty, and frailty over time, depending on disease progression, interventions, and overall health status. This has clinical implications, as early identification of pre-frailty may allow for targeted interventions to prevent further decline.

From a practical perspective, the lack of a single standardized definition remains a challenge. Different tools may identify different patient groups, and no universal threshold exists. However, the consistent finding across studies is that frailty, regardless of how it is measured, is strongly associated with worse outcomes.

In summary, frailty is a multidimensional syndrome that can be assessed using different models and tools. Understanding its definition and phenotypes is essential for integrating frailty into cardiovascular risk assessment and clinical decision-making.

### 3. Pathophysiology of Frailty in Cardiovascular Disease

Frailty in cardiovascular patients results from the interaction of multiple biological processes, including chronic inflammation, neurohormonal activation, metabolic dysregulation, and progressive loss of skeletal muscle mass. These mechanisms overlap with the pathophysiology of cardiovascular disease, which explains their frequent coexistence and mutual reinforcement [7].

Chronic low-grade inflammation is a central feature of frailty. Elevated levels of inflammatory markers such as interleukin-6 and C-reactive protein are consistently observed in frail individuals. In cardiovascular disease, this inflammatory state contributes to endothelial dysfunction, atherosclerosis progression, and myocardial remodeling. The persistence of systemic inflammation accelerates both frailty and cardiovascular deterioration [7].

Neurohormonal activation represents another key mechanism. In conditions such as heart failure, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system leads to catabolic effects, including muscle wasting and impaired energy balance. Over time, this contributes to reduced physical capacity and increased vulnerability to stressors, which are hallmarks of frailty [8].

Sarcopenia plays a central role in the development of frailty. Loss of skeletal muscle mass and strength reduces functional capacity and limits the ability to recover from acute illness. In cardiovascular patients, sarcopenia is often exacerbated by reduced physical activity, chronic disease burden, and metabolic abnormalities. This creates a cycle of inactivity, muscle loss, and further functional decline [8]. Mitochondrial dysfunction and impaired energy metabolism also contribute to frailty. Reduced efficiency of energy production leads to early fatigue, decreased exercise tolerance, and impaired cellular repair mechanisms. These changes are particularly relevant in heart failure, where energy imbalance is a key component of disease progression. Another important factor is nutritional imbalance. Inadequate protein intake and unintentional weight loss are common in frail patients and further accelerate muscle wasting. This is often combined with anabolic resistance, where the body's ability to build and maintain muscle is reduced despite adequate nutritional intake.

Endothelial dysfunction and microvascular impairment further link frailty to cardiovascular disease. Reduced vascular responsiveness limits tissue perfusion and contributes to organ dysfunction, including skeletal muscle impairment. This mechanism reinforces the connection between vascular health and physical performance. Importantly, these processes do not act in isolation. They form a self-perpetuating cycle in which cardiovascular disease promotes frailty, and frailty in turn worsens cardiovascular outcomes. This bidirectional relationship explains why frailty is associated with increased mortality, higher hospitalization rates, and reduced response to therapy.

In summary, frailty in cardiovascular patients reflects a complex interaction of inflammatory, neurohormonal, metabolic, and musculoskeletal mechanisms. Understanding these pathways is essential for recognizing frailty as a biological condition rather than a purely functional or age-related state.

### 4. Frailty and Cardiovascular Outcomes

Frailty is a strong and consistent predictor of adverse outcomes in cardiovascular patients. Its impact extends across different disease states, including heart failure, coronary artery disease, and valvular heart disease, and remains significant even after adjustment for traditional risk factors.

In patients with heart failure, frailty is associated with increased mortality and higher rates of hospitalization. Observational studies show that frail patients have a markedly worse prognosis compared to non-frail individuals, independent of ejection fraction and standard clinical parameters. The presence of frailty reflects reduced physiological reserve, which limits the ability to compensate during disease exacerbations [9].

Frailty also affects outcomes in coronary artery disease. In patients with acute coronary syndromes, frailty is linked to higher in-hospital mortality, increased complications, and prolonged recovery. Importantly, frail patients are less likely to receive invasive management, which may further contribute to worse outcomes [10].

In the context of interventional cardiology, frailty has a major prognostic role. It is one of the strongest predictors of outcomes after procedures such as transcatheter aortic valve implantation (TAVI). Frail patients undergoing TAVI have higher mortality rates, increased procedural complications, and less functional improvement compared to non-frail patients [11]. Beyond mortality, frailty is associated with reduced quality of life and functional decline. Patients with frailty are more likely to experience loss of independence, decreased mobility, and impaired daily functioning. These outcomes are clinically relevant, particularly in elderly populations where maintaining functional status is a key treatment goal.

Another important aspect is the interaction between frailty and guideline-directed therapy. Frail patients are less likely to receive optimal medical treatment, often due to concerns about tolerability and adverse effects. Even when therapy is initiated, dose optimization may be limited. This contributes to a gap between evidence-based recommendations and real-world outcomes.

Frailty also predicts readmissions and healthcare utilization. Studies show that frail cardiovascular patients have higher rates of recurrent hospitalizations and longer hospital stays. This has implications not only for individual prognosis but also for healthcare systems.

Importantly, frailty provides prognostic information beyond traditional risk scores. Standard cardiovascular risk models do not fully capture the multidimensional vulnerability associated with frailty. Incorporating frailty assessment into clinical practice may improve risk stratification and guide treatment decisions.

In summary, frailty is a powerful predictor of mortality, morbidity, and functional decline in cardiovascular patients. Its impact is consistent across different clinical settings and highlights the need for its systematic assessment in routine care.

### 5. Frailty in Heart Failure

Frailty is highly prevalent in patients with heart failure and represents a key determinant of prognosis. Estimates suggest that between 30% and 50% of patients with chronic heart failure meet criteria for frailty, with even higher rates in advanced stages of the disease [12].

The relationship between frailty and heart failure is bidirectional. Heart failure promotes frailty through reduced cardiac output, chronic inflammation, neurohormonal activation, and physical inactivity. At the same time, frailty worsens heart failure outcomes by limiting physiological reserve and reducing the ability to respond to treatment [13]. Clinically, frail patients with heart failure present with reduced exercise tolerance, muscle weakness, and increased fatigue. These features often overlap with symptoms of heart failure itself, making the identification of frailty more challenging. However, the presence of frailty indicates a more advanced and complex disease state.

Frailty has a significant impact on prognosis in heart failure. Studies consistently show higher mortality rates, increased hospitalizations, and poorer functional outcomes in frail patients compared

to non-frail individuals. Importantly, this effect is independent of left ventricular ejection fraction, suggesting that frailty provides additional prognostic information beyond traditional measures [12].

Frailty also influences response to therapy. Patients with frailty are less likely to tolerate guideline-directed medical therapy at target doses. Hypotension, renal dysfunction, and adverse effects are more common, which often leads to dose reduction or discontinuation. As a result, these patients may not receive the full benefit of evidence-based treatment [13]. Another important aspect is the impact of frailty on disease trajectory. Frail patients tend to experience more frequent decompensations and a faster decline in functional status. Recovery after hospitalization is often incomplete, leading to progressive loss of independence and quality of life.

From a therapeutic perspective, the management of frailty in heart failure requires a multidimensional approach. In addition to pharmacological treatment, interventions such as physical rehabilitation, nutritional support, and optimization of comorbidities play a critical role. These strategies aim to improve functional capacity and partially reverse or stabilize frailty. In recent years, there has been growing interest in integrating frailty assessment into heart failure management algorithms. Identifying frailty early may help tailor treatment intensity, guide decision-making, and improve overall outcomes.

In summary, frailty is a common and clinically relevant condition in heart failure. It modifies disease presentation, influences treatment tolerance, and is strongly associated with adverse outcomes. Recognizing frailty is essential for a more individualized and effective approach to heart failure management.

### **6. Frailty and Interventional Cardiology**

Frailty has become a key consideration in interventional cardiology, particularly in elderly patients undergoing transcatheter or surgical procedures. In this setting, chronological age alone is no longer sufficient for risk assessment. Frailty provides additional prognostic information by identifying patients with reduced physiological reserve who may be less likely to benefit from invasive treatment [14]. The best-studied field is transcatheter aortic valve implantation. Patients referred for TAVI are often elderly and multimorbid, which makes frailty highly prevalent in this population. Multiple studies have shown that frailty is associated with higher short-term and long-term mortality after TAVI, as well as with lower functional recovery and poorer quality of life [14]. This means that a technically successful procedure does not always translate into a meaningful clinical benefit in frail patients.

Frailty also affects outcomes after cardiac surgery. In patients undergoing coronary artery bypass grafting or surgical valve replacement, frailty is associated with increased postoperative complications, longer hospital stay, and delayed recovery. These patients are more likely to develop delirium, infections, prolonged immobility, and loss of independence after surgery [15].

In percutaneous coronary intervention, frailty has a similar prognostic role. Frail patients with acute coronary syndromes or stable coronary disease have higher rates of bleeding, procedural complications, readmissions, and mortality after PCI. At the same time, they are less likely to be referred for invasive treatment, reflecting the difficulty of balancing procedural benefit against overall vulnerability [16].

An important clinical issue is that frailty should not be interpreted as an automatic reason to avoid intervention. Rather, it should be used to refine patient selection and to define realistic treatment goals. In some patients, the aim may be survival benefit. In others, preservation of function, symptom relief, or avoidance of repeated hospitalizations may be more relevant endpoints. Frailty assessment is also useful in preprocedural planning. Identifying frailty before intervention may prompt nutritional optimization, physical prehabilitation, closer perioperative monitoring, and better discharge planning. This approach may reduce complications and improve recovery.

Another practical implication is shared decision-making. In frail cardiovascular patients, the expected benefit of intervention must be weighed against the risk of limited recovery and functional decline. Frailty helps frame this discussion in a more individualized and clinically meaningful way.

In summary, frailty is a major determinant of outcome in interventional cardiology. It influences survival, recovery, procedural risk, and post-intervention function. Its assessment should be considered an essential part of the evaluation of patients undergoing TAVI, PCI, or cardiac surgery.

### **7. Frailty and Guideline-Directed Medical Therapy**

Frailty has a direct impact on the use of guideline-directed medical therapy in cardiovascular patients. Although current guidelines are based on large randomized trials, frail individuals are often underrepresented in these studies. As a result, the applicability of trial-based treatment strategies to frail patients is not always straightforward [17].

In routine practice, frail patients are less likely to receive full evidence-based therapy and less likely to reach target doses. This is particularly evident in heart failure, where hypotension, renal dysfunction, electrolyte imbalance, and reduced tolerance often limit up-titration of recommended drugs. In many cases, physicians adopt a more cautious approach, which may be clinically understandable but can also lead to undertreatment [18]. This creates a therapeutic paradox. Frail patients usually have the highest absolute risk and therefore the greatest potential to benefit from effective cardiovascular therapy. At the same time, they are the group in whom treatment is most often reduced, delayed, or avoided because of concerns about tolerability and adverse events.

Polypharmacy adds another layer of complexity. Most frail cardiovascular patients have multimorbidity and receive multiple medications simultaneously. This increases the risk of drug interactions, side effects, poor adherence, and prescribing cascades. In such patients, the challenge is not only to apply guidelines, but to adapt them without losing their core therapeutic benefit [19]. Frailty also affects therapeutic goals. In robust patients, treatment strategies are often focused on long-term event reduction and survival. In frail patients, maintaining function, reducing symptoms, preventing hospitalization, and preserving quality of life may become equally important or even dominant priorities. This shifts the emphasis from disease-centered treatment to patient-centered care.

An important practical point is that frailty should not automatically justify therapeutic nihilism. The presence of frailty does not mean that evidence-based therapy should be withheld. Rather, it calls for closer monitoring, slower titration when needed, and more individualized risk-benefit assessment. In some cases, simplified regimens and careful prioritization of high-value therapies may be more effective than strict pursuit of maximal drug intensity. There is growing recognition that frailty assessment should be integrated into treatment planning. Identifying frailty early may help clinicians distinguish between patients who are likely to tolerate standard treatment pathways and those who require modified strategies, multidisciplinary support, or closer follow-up.

In summary, frailty significantly influences the implementation of guideline-directed medical therapy. It is associated with lower treatment intensity, reduced dose optimization, and greater clinical uncertainty. A frailty-informed approach may improve the balance between evidence-based treatment and real-world tolerability.

### **8. Frailty, Multimorbidity and Real-World Cardiovascular Patients**

Frailty is most clinically relevant in the context of multimorbidity, which characterizes the majority of real-world cardiovascular patients. Unlike participants in randomized trials, these patients frequently present with overlapping conditions such as heart failure, chronic kidney disease, diabetes, atrial fibrillation, and cognitive impairment. Frailty represents the clinical expression of this accumulated burden and reflects the overall biological vulnerability of the patient [20]. The interaction between frailty and multimorbidity is complex and bidirectional. Chronic diseases contribute to functional decline, inflammation, and metabolic imbalance, all of which promote frailty.

In turn, frailty worsens disease outcomes by reducing physiological reserve, impairing recovery, and limiting tolerance to treatment. This interaction leads to a cycle of progressive deterioration that is often observed in advanced cardiovascular disease. In real-world practice, frailty modifies the presentation of cardiovascular conditions. Symptoms may be atypical, less pronounced, or masked by general functional decline. For example, reduced physical activity due to frailty may obscure classical symptoms such as exertional dyspnea or angina, delaying diagnosis and treatment.

Frailty also influences clinical decision-making in complex patients. In individuals with multiple comorbidities, the focus often shifts from disease-specific targets to overall functional status and quality of life. This requires a more holistic approach, where therapeutic strategies are individualized rather than strictly guideline-driven. An important aspect is the relationship between frailty and healthcare utilization. Frail patients with multimorbidity have higher rates of hospitalization, longer hospital stays, and increased risk of readmission. These outcomes are driven not only by the severity of cardiovascular disease but also by the limited ability to recover after acute events.

Polypharmacy is a common consequence of multimorbidity and further complicates management. Frail patients are particularly vulnerable to adverse drug reactions, drug–drug interactions, and poor adherence. This creates a need for careful medication review and prioritization of therapies with the highest clinical value.

Another key issue is functional decline. In frail patients, even minor clinical events can lead to significant loss of independence. Recovery is often incomplete, and repeated hospitalizations may accelerate deterioration. This highlights the importance of early identification and intervention in pre-frail stages. From a practical perspective, the management of frailty in multimorbid cardiovascular patients requires a multidisciplinary approach. Collaboration between cardiologists, geriatricians, primary care physicians, and rehabilitation specialists is essential for optimizing outcomes.

In summary, frailty represents the clinical interface between cardiovascular disease and multimorbidity. It captures the complexity of real-world patients and provides a more comprehensive framework for understanding risk, guiding treatment, and improving patient-centered care.

### 9. Clinical Challenges and Practical Implementation

Despite increasing recognition of frailty as a key determinant of outcomes in cardiovascular patients, its integration into routine clinical practice remains inconsistent. Several challenges limit its widespread implementation, including lack of standardization, time constraints, and uncertainty regarding how to act on frailty assessment results. One of the main issues is the absence of a universally accepted assessment tool. Multiple instruments are available, such as the frailty phenotype, the frailty index, and the Clinical Frailty Scale, each capturing different aspects of vulnerability. While all are predictive of adverse outcomes, variability between tools complicates comparison and limits uniform adoption in clinical practice [17]. Time and workflow constraints also play an important role. Comprehensive frailty assessment may be perceived as time-consuming, particularly in busy cardiology settings. As a result, frailty is often assessed informally or not at all. However, simpler tools such as the Clinical Frailty Scale offer a practical alternative and can be incorporated into routine evaluation with minimal burden.

Another challenge is translating frailty assessment into clinical decisions. Identifying a patient as frail does not automatically define the optimal therapeutic strategy. Clinicians must interpret frailty in the context of overall clinical status, disease severity, and patient preferences. This requires a shift from standardized treatment algorithms toward individualized decision-making.

Risk stratification is another area of uncertainty. Traditional cardiovascular risk models do not include frailty, which may lead to underestimation of risk in vulnerable patients. Incorporating frailty into risk assessment could improve prognostic accuracy, but validated integrated models are still lacking.

## Science & Research

Communication and shared decision-making are particularly important in frail patients. Treatment goals may differ from those in younger or more robust individuals. Discussions should include not only survival but also quality of life, functional status, and patient priorities. Frailty assessment provides a framework for these conversations.

There are also challenges related to therapeutic intensity. Clinicians must balance the potential benefits of treatment against the risk of adverse effects and functional decline. In some cases, less intensive but more tolerable strategies may be appropriate. In others, maintaining guideline-directed therapy with closer monitoring may provide better outcomes.

From a systems perspective, implementation of frailty assessment requires a multidisciplinary approach. Collaboration between cardiology, geriatrics, rehabilitation, and primary care is essential. Structured pathways that include frailty screening, risk stratification, and tailored interventions may improve both clinical outcomes and healthcare efficiency. Finally, there is a need for further research. Most available data are observational, and randomized trials specifically addressing frail cardiovascular patients are limited. Future studies should focus on how frailty-guided strategies affect outcomes, including mortality, hospitalization, and quality of life.

In summary, frailty assessment offers clear clinical value but faces practical and conceptual challenges. Overcoming these barriers is essential for integrating frailty into modern cardiovascular care.

### 10. Conclusion

Frailty has emerged as a critical determinant of outcomes in cardiovascular patients, reflecting biological vulnerability rather than chronological age. It integrates multiple domains, including physical performance, comorbidity burden, and functional reserve, providing a more comprehensive assessment of patient risk.

Across a wide spectrum of cardiovascular conditions, frailty is consistently associated with increased mortality, higher hospitalization rates, reduced tolerance to therapy, and poorer functional outcomes. Its impact is particularly evident in heart failure and interventional cardiology, where it significantly influences both short-term and long-term prognosis.

Current clinical practice remains limited by inconsistent assessment and lack of standardized integration into decision-making pathways. However, the growing body of evidence supports the routine incorporation of frailty evaluation into cardiovascular care. Even simple tools can provide meaningful prognostic information and improve risk stratification.

Importantly, frailty should not be interpreted as a contraindication to treatment, but rather as a factor guiding individualized therapeutic strategies. In this context, management shifts from a disease-centered approach to a patient-centered model, where treatment goals include not only survival but also functional preservation and quality of life.

Future research is needed to define optimal frailty-guided interventions and to determine whether targeted strategies can improve clinical outcomes. The integration of frailty into clinical guidelines and routine practice represents a key step toward more personalized cardiovascular medicine.

#### 1. References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146–M156. DOI: 10.1093/gerona/56.3.M146 PMID: 11253156;
2. Afilalo J, et al. Frailty in cardiovascular disease. *J Am Coll Cardiol.* 2014;63(8):747–762. DOI: 10.1016/j.jacc.2013.09.070 PMID: 24291279;
3. Singh M, et al. Frailty and outcomes after cardiovascular interventions. *Circulation.* 2014;130:1482–1492. DOI: 10.1161/CIRCULATIONAHA.114.011282 PMID: 25266293;
4. Fried LP, Tangen CM, Walston J, et al. Frailty phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56:M146–M156. DOI: 10.1093/gerona/56.3.M146 PMID: 11253156;

## Science & Research

6. Rockwood K, Mitnitski A. Frailty index based on deficit accumulation. *J Gerontol A Biol Sci Med Sci.* 2007;62(7):722–727. DOI: 10.1093/gerona/62.7.722 PMID: 17634318;
7. Rockwood K, Song X, MacKnight C, et al. Clinical Frailty Scale. *CMAJ.* 2005;173(5):489–495. DOI:10.1503/cmaj.050051 PMID: 16129869;
8. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet.* 2013;381:752–762. DOI:10.1016/S0140-6736(12)62167-9 PMID: 23395245;
9. Anker SD, Morley JE, von Haehling S. Cachexia and sarcopenia in heart failure. *Lancet.* 2016;387:2636–2646. DOI: 10.1016/S0140-6736(16)31078-9 PMID: 27160515;
10. Lupón J, González B, Santa Eugenia S, et al. Prognostic implication of frailty in chronic heart failure. *Eur J Heart Fail.* 2008;10(12):1251–1256. DOI: 10.1016/j.ejheart.2008.09.011 PMID: 19019601;
11. Ekerstad N, Swahn E, Janzon M, et al. Frailty and outcomes in acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care.* 2011;1(2):113–120. DOI: 10.1177/2048872612451164 PMID: 24062854;
12. Afilalo J, et al. Frailty in patients undergoing TAVI. *J Am Coll Cardiol.* 2012;60(8):689–700. DOI:10.1016/j.jacc.2012.06.011 PMID: 22818063
13. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure. *Heart Fail Rev.* 2017;22(3):357–366. DOI: 10.1007/s10741-017-9599-5 PMID: 28120286;
14. Vitale C, Jankowska E, Hill L, et al. Frailty in heart failure: clinical implications. *Eur J Heart Fail.* 2019;21(11):1299–1306. DOI:10.1002/ejhf.1615 PMID: 31483079;
15. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* 2012;5(9):974–981. DOI: 10.1016/j.jcin.2012.06.011 PMID: 22995734;
16. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg.* 2014;148(6):3110–3117. DOI: 10.1016/j.jtcvs.2014.07.087 PMID: 25199837;
17. Dodson JA, Hochman JS, Roe MT, et al. Frailty and outcomes among older patients with acute myocardial infarction treated with PCI. *J Am Heart Assoc.* 2018;7(10):e008101. DOI: 10.1161/JAHA.117.008101 PMID: 29724811;
18. Afilalo J, et al. Frailty assessment in cardiology. *J Am Coll Cardiol.* 2014;63:747–762. DOI: 10.1016/j.jacc.2013.09.070 PMID: 24291279;
19. Vidán MT, et al. Frailty and HF outcomes. *Eur J Heart Fail.* 2016;18:869–875. DOI: 10.1002/ejhf.518 PMID: 26888567;
20. Kim DH, et al. Frailty and polypharmacy. *J Gerontol A Biol Sci Med Sci.* 2018;73:980–987. DOI: 10.1093/gerona/glx229 PMID: 29149269;
21. Clegg A, et al. Frailty overview. *Lancet.* 2013;381:752–762. DOI: 10.1016/S0140-6736(12)62167-9 PMID: 23395245.